REMARKS

Claims 1 through 27 are currently pending in the present application. Claims 1-2, 4-5, 7, and 13-15 have been amended. Claims 16-27 have been added. No new matter is introduced in the application by these amendments.

Rejection Under 35 U.S.C. 112, First Paragraph

Claims 1-15 stand rejected under 35 U.S.C. 112, first paragraph. The Examiner alleges lack of written description.

The present invention relates to end-modification of an aptamer by a protein with the result that the half-life of the modified aptamer in the circulation is extended. Applicants assert that the present specification adequately describes the common structural feature, i.e. modification of the 5′ or 3′ end of a nucleic acid by a protein, that provides for this result. The particular sequence of the aptamer nucleic acid is not particularly relevant to the present invention. Furthermore, a large number of variations of the nucleotide sequence aptamers that bind to at least the blood clotting protein thrombin are well known in that art and thus need not be described in detail in the specification. Therefore, Applicants respectfully request withdrawal of the 35 U.S.C. 112 rejection.

Rejection Under 35 U.S.C. 103(a)

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffin et al. in view of Boado et al. Griffin discloses aptamers that bind to thrombin and Boado is cited for teaching 5′ and 3′ end modification by avidin-biotin for the protection of oligonucleotides against serum nuclease degradation. This rejection is respectfully traversed as applied to the new and amended claims.

The Examiner cites the combination of the teachings of Griffin and Boado to modify thrombin specific aptamers using the avidin-biotin system for nuclease protection in serum and therefore rejects claims 1-15 under 103(a). This rejection is traversed. In particular, the Examiner fails to establish *prima facie* obviousness of the claimed invention in view of the cited references. In particular, the combined references do not disclose or suggest every element of the claimed invention. Furthermore, there is no motivation to combine the references in the manner suggested by the Examiner. Applicants respectfully point out the deficiencies in the Examiner's argument as to claims 1-15. First, Boado only discloses using avidin and not streptavidin. Second, neither Griffin nor Boado teach use of avidin for extending half-life of a nucleic acid *in vivo*. Finally, as to claims 16-27, neither Boado

nor Griffin disclose or suggest use of a 2'-fluoropyrimidine or 2'-aminopyrimidine RNA nucleic acid.

Using Avidin Versus Streptavidin

One of the intentions of the present invention is using aptamer nucleic acids in the blood circulation for therapeutic purposes. It requires that the oligonuclotide exert its effect in the intercellular fluids or in a compartment such as the blood - that is, outside of cells - and therefore it must have an appropriate half-life *in vivo*. The present invention has shown that the use of streptavidin or variants thereof confers the unexpected result that the protected aptamer has a much longer half-life *in vivo* than an aptamer protected by avidin. As disclosed on page 7 of the specification as filed, streptavidin has a natural half-life of 2.5 hours in the circulation of rats and rabbits; whereas its homolog, avidin, is rapidly cleared from circulation.

Boado discloses only the use of avidin to inhibit degradation of oligonucleotides by serum nucleases. However, avidin has some properties, principally its being cleared from intercellular fluids and the blood by endocytosis, that make it unsuitable for use in the present invention. These unsuitable properties of avidin are demonstrated by its short half-life in blood - about 20 seconds. (*See*, Rosebrough, *Nucl. Med. Biol.* 20:663, esp. Figure 1, submitted

with IDS filed September 10, 2001) The short half-life of avidin *in vivo* is not predictable based upon the ability of avidin to protect a nucleic acid from nuclease attack *in vitro*.

The uptake of avidin by endocytosis makes it an excellent protector and facilitator of transmembrane transport for oligonucleotides used for antisense therapeutics, as disclosed in Boado. However, it is because of this same reason that avidin is completely useless for the present invention, which requires that the protected oligonucleotide remain in the blood long enough to bind to a blood clot for imaging or therapeutic purposes. Therefore, there is no motivation to replace avidin with streptavidin or variants thereof as in the present invention.

Present Invention Seeks To Lengthen Half-Life In Vivo, Not Nuclease Protection

The Examiner alleges that combining the teachings of Griffin and Boado would motivate one to develop thrombin specific aptamers using the avidin-biotin system to provide nuclease protection in serum. As previously discussed, there is no motivation in Griffin nor Boado to use avidin in place of streptavidin or variants thereof. Additionally, nowhere in Griffin nor Boado does it teach the goal of the present invention which is to provide the result of lengthening the half-life of the aptamer *in vivo*.

The Examiner cites Griffin for teaching methods of separating target/apatamer complexes using biotin and avidin. Boado uses a biotin-avidin system for nuclease protection. Combining these teachings does not result in using biotin and streptavidin for lengthening aptamer half-life *in vivo*. The combination of the two references provides no motivation to insert biotin directly into the aptamer sequence to address the problem of *in vivo* stability in circulating blood nor does it provide an approach for slowing aptamer clearance *in vivo*.

The present invention discloses the preferred aptamer type as DNA, 2'-fluoropyrimidine RNA or 2'-aminopyrimidine RNA. Although Griffin states that single strand DNA is the preferred aptamer, DNA is not the sole backbone material taught by the present invention. Griffin states DNA is the preferred aptamer, especially because DNA is more resistant to serum nuclease than is RNA. Neither Griffin nor Boado disclose or suggest the innovative RNA analogs, 2'-fluoropyrimidine RNA or 2'-aminopyrimidine RNA, and their usefulness in aptamer stabilization *in vivo*.

Conclusion

In order to establish a *prima facie* case of obviousness, the Examiner must demonstrate three basic criteria: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art, to modify the reference(s) or to combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference(s) must teach or suggest all the claim limitations.

The Examiner has not successfully made a case of *prima facie* obviousness because: 1) there is no motivation to combine the references to modify thrombin specific aptamers for the intention of lengthening their half-life *in vivo*; 2) replacing streptavidin, or variants thereof, in the present invention with avidin as taught by the references does not successfully lengthen the half-life of aptamers *in vivo* for the purposes of the invention; and 3) the references do not teach every aspect of the claimed invention, particularly modifying aptamers with streptavidin, or variants thereof, or the use of RNA analogs as nucleosides. Applicants respectfully request, therefore, that the 103(a) rejection be withdrawn.

If the Examiner has any questions regarding the above matters, please contact Applicants' representative, Mark J. Nuell, Ph.D., at the telephone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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4045-0109P

Attachments: Version with markings to show changes made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The following claims have been amended as follows:

1. (Amended) A composition comprising:

a nucleic acid that binds to a blood clot or to a protein that is a component of a mammalian blood clotting cascade; and

a protein ~~complexed~~ attached to said nucleic acid at either the 5' end or the 3' end or both wherein said protein is streptavidin or a variant of streptavidin that retains biotin binding activity.

2. (Amended) The composition of claim 1, wherein said nucleic acid is derivatized at the 5' or 3' end or at both the 5' and 3' ends with a reagent specific for ~~complexing~~ binding to said protein thereby forming a ~~and said~~ complex ~~is formed by~~between said reagent and said protein.

4. (Amended) The composition of claim 2, wherein said reagent is biotin ~~and said protein is streptavidin or a variant of streptavidin that retains biotin binding activity~~.

5. (Amended) The composition of claim 3, wherein said reagent is biotin that is covalently attached to ~~said~~ a linker ~~and said protein complexed thereto is streptavidin or a variant of strepavidin that retains biotin binding activity~~.

7. (Amended) The composition ~~of claim~~ of any one of claims 1-6, wherein said nucleic acid is DNA, 2'-fluoropyrimidine RNA or 2'-aminopyrimidine RNA.

13. (Amended) A method for inhibiting degradation of a nucleic acid in the blood comprising ~~complexing~~ attaching streptavidin or a variant thereof that retains biotin binding activity to said nucleic acid at the 5' or 3' end or at both the 5' and 3' ends. ~~with a protein.~~

14. (Amended) The method of claim 13, wherein said nucleic acid is derivatized with biotin ~~and said protein is streptavidin or a variant thereof that retains biotin binding activity~~.

15. (Amended) The method of claim ~~12 or~~ 13 wherein said nucleic acid is DNA, 2'-fluoropyrimidine RNA or 2'-aminopyrimidine RNA.

Claims 16 through 27 have been added.